REMARKS

The Office Action dated June 15, 2004 has been received and carefully studied.

A Request for Continued Examination is filed herewith.

The Examiner maintains the rejection of claims 6-15 and 18-20 under 35 U.S.C. §103(a) as being unpatentable over Polivka I or Polivka II in view of Le Bigot and Bourquin and Kofler. The Examiner admits that Polivka I and II do not specifically disclose the enantiomers of norketotifen, hydroxy ketotifen and hydroxy-norketotifen, but states that administration of a pure enantiomer of ketotifen to an animal would lead to the corresponding compound, since they are known metabolites as shown by Bigot. The Examiner also considers that the lack of sedative side effects of the S-enantiomeric form of the norketotifen metabolite is intrinsic to the compound.

The rejection is respectfully traversed.

As an initial matter, the Examiner is respectfully requested to specifically address Applicant's arguments regarding claim 6. The Examiner has yet to point out where in any of the cited references the method of synthesis recited in claim 6 is disclosed or suggested. All of the Examiner's comments with respect to this rejection discuss the methods of treating diseases; nowhere is the method of claim 6 addressed. Claim 6 recites that the corresponding isomer of ketotifen is converted to its intermediate, followed by cleavage catalyzed with Cd/Pb under mild

conditions. This method is not obvious, nor has it been disclosed for the related demethylation of racemic ketotifen to give racemic norketotifen. The published method of Waldvogel et al. (copy enclosed by way of an Information Disclosure Statement) is too harsh to apply to a ketotifen enantiomer without causing racemization of the end product because of the high temperature required. The Cd/Pb catalyzed method has been developed to avoid racemization, and is nowhere disclosed or suggested by the cited art. Indeed, Example 3 of Bourquin teaches the synthesis of 10-hydroxy ketotifen. It is not converted to its nor-intermediate, and Cd/pb is not used. Accordingly, the instant synthetic method is nowhere disclosed or suggested.

With reference to claims 7-15 and 18-20, none of the cited references, alone or in combination, discloses or suggests the administration of an effective amount of the S-isomer of norketotifen for the treatment of the diseases recited. Indeed, prior to the present invention, it was not known that the S-isomer of norketotifen even existed. How, then, can there be a suggestion to administer a therapeutically effective amount of a compound that was not known to exist?

Reference to *Schering Corp. v. Geneva Pharmaceuticals Inc.*, 67 U.S.P.Q.2d 1664 (Fed. Cir. 2003) is instructive. In *Schering*, the Federal Circuit held that claims directed to the metabolite desloratadine itself were invalid in view of prior art that disclosed the parent compound loratadine. The Court reasoned that

the prior patent to loratadine inherently disclosed the metabolite. However, the Court expressly stated that patent protection is available for metabolites if claimed in pure and isolated form, or if claimed as methods of administration:

> "A skilled patent drafter, however, might fashion a claim to cover the metabolite, in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in *Kratz* and *Bergstrom*, or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition."

67 U.S.P.Q.2d at 1670. What is even more compelling in the instant case is that the claims to a method of administration recite administration of an isomer that was not known to exist. In *Schering*, administration of loratadine would lead to desloratidine, but this did not preclude patentability of the method, since such adminstration was not disclosed (either inherently or expressly) or suggested by the prior art. Similarly, although in the present case administration of the S-enantiomer of ketotifen would lead to S-norketotifen, such administration is nowhere disclosed or suggested by the cited art. Indeed, the cited art also does not suggest the instantly claimed methods because the fact that norketotifen is chiral, exhibits atropisomerism, and has stereoisomers was not known. In addition, the present inventor unexpectedly found that the S-isomer is free from sedative side effects, and is twice as potent as the R-isomer

as an anti-inflammatory agent.

Accordingly, claims 7 and 20, and claims dependent thereon, are believed to be allowable, since none of the cited references discloses or suggests that the diseases recited could be effectively treated or prevented by administering the S-isomer of norketotifen while eliminating the dose-limiting sedative side effects of ketotifen.

The Examiner rejects claims 7, 13-15 and 18-20 under 35 U.S.C. §112, first paragraph, as being non-enabling. The Examiner states that the specification does not enable the use of the compounds to treat or prevent the diseases recited.

By the accompanying amendment, claim 7 has been amended to recite treatment of allergic disorders and inflammatory disorders of the skin, the respiratory tract and the gastrointestinal tract. S-norketotifen has been found to express potent antihistaminic and potent anti-inflammatory activities and all of the diseases now recited are allergic and/or inflammatory diseases. Applicants respectfully submit that the skilled artisan would have a reasonable expectation that administration of this compound (administration of a compound with the pharmacological properties that have now been found for S-norketotifen), would be effective for treating the disorders recited. Claim 20 has been cancelled.

The Examiner rejects claims 1, 6-15 and 18-20 under 35 U.S.C. §102(a) as being anticipated by Aberg I, WO 98/56381 or Aberg II, WO 98/43640.

By the accompanying amendment, claims 1 and 7 have been amended to recite that the compound administered is substantially free from the racemate and the corresponding R-isomer. It is believed that the amendment overcomes the rejection.

The Examiner also rejects claims 7, 9, 10, 12, 13-15 and 18-20 under the judicially created doctrine of obviousness-type double patenting of claims 1-7 of U.S. Patent No. 6,207,684.

By the accompanying amendment, claim 7 has been amended to delete ocular disorders. Claim 12 has been cancelled. It is believed that the amendment overcomes the rejection.

New claim 21 has been added to further define the invention.

Reconsideration and allowance are respectfully requested in view of the foregoing.

Respectfully submitted,

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